Exploring Second-Generation CLL Inhibitors

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Andrew Schorr:
So you taught us about BTK inhibitors, and we heard about PI3K inhibitors. You mentioned those. So we have drugs for that now. But there are second-generation ones, and then there's this SyK inhibitor, Lyn inhibitor, other kind of inhibitors. So second generation, what's the benefit of second-generation drugs?

Dr. Lamanna:
So, I mean, as we've learned about ibrutinib (Imbruvica) and idelalisib (Zydelig), clearly the companies—we're now learning about the toxicities of these drugs and how they could be limiting to certain individuals. And so obviously, different pharmaceutical companies are going back to the drawing board and seeing, well, okay, we know this is effective in CLL. So can we make the drugs safer? Can we have less side effects? Can we, instead of what Phil talked about before with these off-target effects, can we have these molecules designed, so they don't hit some of these off-target molecules and cause some of these side effects such as atrial fibrillation, or bruising, or hypertension or whatever? And so now, many companies are actually—there are many drugs being looked at that are what we call second-generation BTK inhibitors and PI3 kinase inhibitors looking to improve upon the two already approved drugs, which is ibrutinib and idelalisib. So stay tuned, because there are some that are going head to head with the competition to see if the side effects will be less than the currently already available drugs.

And so they'll be important because obviously if the toxicity's less, that gives a broader range of availability to you all.

Andrew Schorr:
Okay. So we mentioned about the off-target effects. You said it first, Phil. So somebody comes to you, and you have a trial going on for one of these. You may say, "Let's see if this is tomorrow's medicine today for you that may be more elegant, if you will, more refined. But we don't know."

Dr. Thompson:
Yeah. So if someone's able, logistically, to go into one of our clinical trials, definitely, I would recommend doing that. Because we're looking at a number of strategies, either combinations or comparisons with some of these newer inhibitors to see whether we can do better than what we've been doing. Even though these things are good, we've always got to improve.

Andrew Schorr:
Okay. And just so we understand SyK and Lyn. So you're seeing other pathways, I think you call them, that may be responsible for allowing CLL to continue. And so you're saying, do we have a drug that can turn that off, right?

Dr. Lamanna:
Yeah. So these are just other proteins that we're learning to block as well. Fostamatinib is not—we did some studies earlier on that looked very favorable. They actually have a second generation of that, so entospletinib. That's the drug being looked at now, sorry. Just updating your slide. And then Lyn inhibitors, they are also active drugs. Dasatinib's actually approved in a different leukemia and chronic myelogenous leukemia, so that's already available. But they don't seem as promising as single agents, necessarily, so they're looking at some combinations strategies with those as well.